

# Current Therapeutic Options and Treatments in Development for the Management of Primary Open-Angle Glaucoma

Jeffrey M. Liebmann, MD, FACS, and Jeannie K. Lee, PharmD, FASHP

## Glaucoma: Definition and Associated Risk Factors

Glaucoma comprises a heterogeneous group of chronic, progressive, optic neuropathies characterized by loss of retinal ganglion cells and their axons. Glaucoma results in visual impairment and is the second leading cause of irreversible blindness worldwide.<sup>1,2</sup> Primary open-angle glaucoma (POAG) is the most common type of glaucoma, and is estimated to account for approximately 90% of cases of glaucoma in North America.<sup>3,4</sup> Because symptoms of POAG do not manifest until the disease process is already in advanced stages, and because the progression of disease occurs gradually over the course of many years, POAG is sometimes referred to as the “silent thief of sight.”<sup>5</sup>

Current management guidelines from the American Academy of Ophthalmology Preferred Practice Pattern cite several important risk factors for POAG, including advanced age, African American and Latino/Hispanic ethnicity, elevated intraocular pressure (IOP), family history of glaucoma, low ocular perfusion pressure (OPP), type 2 diabetes, myopia, and having a thinner central cornea.<sup>2</sup>

OPP is defined as the difference between arterial blood pressure and the IOP. Although further investigation is needed, it is thought that low OPP alters blood flow at the optic nerve head, contributing to glaucomatous damage to the optic nerve.<sup>2</sup> Importantly, while glaucoma is associated with several risk factors that contribute to damage and disease progression, IOP is the only proven modifiable risk factor at this time.<sup>3</sup>

## Burden of Glaucoma

### Disease Burden

Globally, glaucoma affects 3.5% of adults 40 to 80 years of age (POAG 3.1% plus angle closure glaucoma [ACG] 0.5%).<sup>4</sup> With the average age increasing worldwide, the incidence of glaucoma in this population of adults is projected to increase by 74% from 2013 to 2040.<sup>4</sup> With this increase in prevalence of glaucoma, the consequences of glaucoma in terms of vision loss are also expected to grow. Worldwide, the number of people experiencing bilateral blindness from primary glaucoma is expected to reach 11.1 million by 2020.<sup>6</sup>

The increasing burden of glaucoma has important implications for the United States health care system. The CDC estimates that

## ABSTRACT

Primary open angle glaucoma (POAG) is the most common type of glaucoma, and is responsible for approximately 90% of glaucoma cases in North America. POAG is characterized by an asymptomatic onset, where patients do not present with symptoms until significant visual loss occurs in late stages of the disease. Importantly, while glaucoma is associated with several risk factors that contribute to damage and disease progression, intraocular pressure (IOP) is the only proven modifiable risk factor at this time. Treatments for POAG include use of pharmacologic and surgical interventions. As of this writing, available pharmacologic options reduce IOP through reduction of aqueous humor production or by facilitating aqueous humor drainage through the uveoscleral outflow pathway (the unconventional pathway). Although cholinergic agonists (eg, pilocarpine) indirectly targets aqueous humor draining through the trabecular meshwork/Schlemm’s canal (the conventional outflow pathway), cholinergic agonists are not frequently used, and as of this writing, no agents are currently available that target both the conventional and unconventional outflow pathways. Therapies in late-stage development include trabodendoson, netarsudil, and latanoprostene bunod.

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For author information and disclosures, see end of text.

in 2015, 2.2 million Americans 40 years and older (about 2% of the population) had glaucoma.<sup>7</sup> Another estimate suggests that by 2050, the number of people in the United States with POAG aged 40 years and older is expected to increase to 7.32 million individuals, a nearly 3-fold increase from the incidence of POAG from 2011.<sup>8</sup>

The prevalence of POAG is highest among individuals of Latino/Hispanic and African heritage.<sup>8</sup> In a 2016 meta-analysis by Kapetanakis et al, researchers estimated the prevalence of POAG among those aged 65 years to be 6.4% and 4.0% in patients of African descent and Latino patients, respectively, versus a prevalence of 2.0% among those of European descent.<sup>9</sup> Moreover, in an adjusted analysis, the risk of developing POAG increases by a factor of 2.3 with each advancing decade among Hispanic patients versus a factor of 1.6 among patients of African descent, and a factor of 2.0 among those of European descent.<sup>9</sup> The Hispanic/Latino population is estimated to contribute to the greatest number of individuals with POAG in the United States over the next 4 decades.<sup>8</sup>

POAG is characterized by an asymptomatic onset, where patients do not present with symptoms until significant visual loss occurs in late stages of the disease. As patients do not have symptoms until visual damage has already occurred, many cases remain undiagnosed and untreated.<sup>2</sup> The National Health and Nutrition Examination Survey published in 2014 found approximately 2.4 million individuals in the United States (2.9% of the US population) had undiagnosed and untreated glaucoma, suggesting that 78% of glaucoma was untreated and undiagnosed.<sup>10</sup> The rate of undiagnosed and untreated glaucoma is estimated to be 85% for blacks, 81% for Hispanics, and 73% for non-Hispanic whites.<sup>10</sup>

## Economic Burden

As a chronic and progressive disease, glaucoma poses a substantial burden to the healthcare system. Management of glaucoma has direct medical costs (eg, visits to providers, tests, medications, and surgery), direct nonmedical costs (eg, home healthcare, and transportation), and indirect costs (eg, loss of productivity for both patient and caregiver).<sup>2</sup>

According to a Prevent Blindness study, the \$6 billion spent annually in 2014 on the direct costs of glaucoma care is expected to reach \$12 billion by 2032, and exceed \$17 billion by 2050.<sup>11,12</sup>

Medicare beneficiaries with glaucoma had higher mean annual total healthcare costs compared with those without glaucoma, and more severe cases of glaucoma in Medicare beneficiaries are associated with higher direct annual costs. One study found that the mean annual total cost of healthcare per patient was \$16,760 among Medicare beneficiaries aged 65 years and older with glaucoma versus \$13,094 for Medicare beneficiaries without glaucoma. The cost increased by severity of disease. Those with visual disability had costs of \$18,073, while those without visual disability had costs of \$15,829. In this population, the primary drivers of cost were physician services, inpatient care, and prescription medications.<sup>13</sup>

## Current Management Options and Unmet Needs

Within the eye, the balance between the production of aqueous humor in the ciliary tissue and outflow of aqueous humor out of the eye through the conventional (ie, the trabecular meshwork and Schlemm's canal) and the unconventional (ie, uveoscleral) pathways functions to maintain an IOP of approximately 10 to 21 mm Hg.<sup>14-18</sup> Current therapies are aimed at either enhancing the outflow of aqueous humor via the unconventional or uveoscleral pathway, or by decreasing the production of aqueous humor.<sup>19</sup> Although muscarinic cholinergic agonists may enhance outflow of aqueous humor through the trabecular meshwork by contracting the ciliary muscle, these agents are used infrequently as they may cause blurry vision and myopia and are subject to adherence challenges (they may be administered up to 4 times daily).<sup>3,14,20</sup> As a result, in practice, there is a lack of agents that target the conventional pathway.<sup>3,20</sup> Existing mechanisms are illustrated in **Figure 1**.<sup>19</sup> Although several mechanisms for IOP-lowering are available, no treatment is available to repair or regenerate optic nerve damage in patients with glaucoma. The goal of POAG management is to lower IOP, since elevated IOP is the only known modifiable risk factor for progressive disease leading to blindness.<sup>20,21</sup> However, lowering IOP may not be sufficient to prevent vision loss, highlighting the need for new agents with new mechanisms of action and perhaps more effective IOP lowering.<sup>1</sup>

Management of glaucoma includes control of IOP to a target pressure of at least a 25% reduction which has been shown to slow progression of POAG. However, an IOP target sufficient to reduce IOP by more than 25% may be selected if there is more severe optic nerve damage, damage is increasing rapidly, or the patient has the risk factors indicated previously. A higher IOP target may be acceptable for patients who do not tolerate treatments or have a limited life expectancy.<sup>2</sup> Of note, approximately one-third to one-half of patients with POAG do not have elevated IOP—a condition known as normal tension glaucoma (NTG).<sup>1,22</sup> NTG is characterized by ocular damage and vision loss at statistically normal intraocular pressure levels (maximum IOP <21 mm Hg). Treatment for patients with NTG also aims to reduce IOP; a 30% reduction of IOP in patients with NTG was shown to slow the rate of visual field progression.<sup>23,24</sup> However, patients with NTG may have difficulty achieving substantial IOP reductions given their low baseline IOP. Additional IOP-lowering is a challenge for patients with NTG in comparison to patients with elevated IOP.<sup>23</sup>

The usual steps for treating glaucoma include the use of instilled medications (eye drops). If pharmacologic treatment is not sufficiently effective, surgical procedures may be required; these include laser surgery (trabeculoplasty or cycloablation), traditional surgery (trabeculectomy), or other procedures (eg, shunts or canaloplasty).<sup>25</sup> As indicated previously, available instilled ophthalmic preparations used in clinical practice are limited to agents that reduce IOP either through reduction of aqueous humor production or by facilitating aqueous

humor drainage (uveoscleral outflow). Although muscarinic agonists indirectly target the conventional outflow pathway by contracting the ciliary muscle to widen and promote outflow through the trabecular meshwork/Schlemm's canal, as of this writing, there are no agents directly targeting the conventional outflow pathway or agents that impact both conventional and unconventional pathways.<sup>3,14,20</sup> As of this writing, there are no available agents targeting both conventional and unconventional outflow pathways for IOP lowering.<sup>3,14</sup>

### Management With IOP-Reducing Therapy

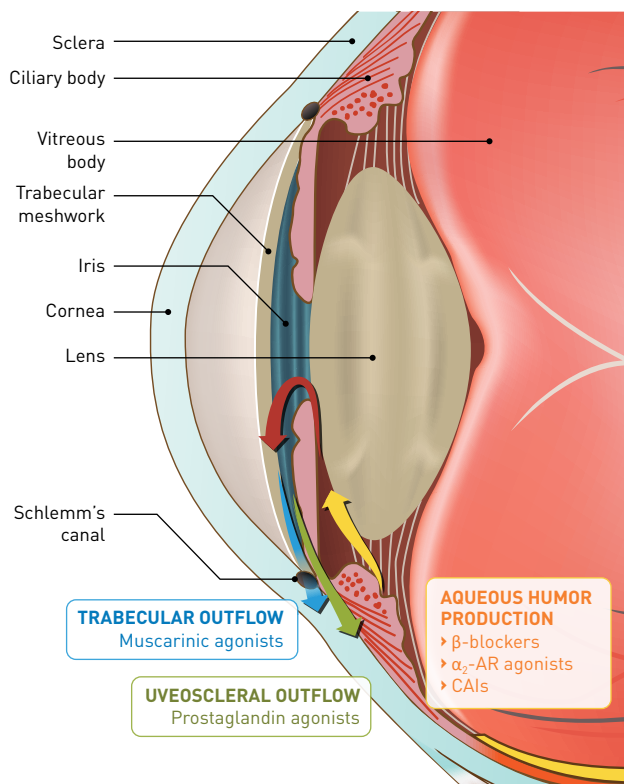
It is well-established that management with IOP-reducing pharmacologic therapy reduces the risk of glaucoma onset in patients with ocular hypertension (OHT) and use of pharmacologic and surgical therapies reduces the risk of disease progression and vision loss in patients with glaucoma.<sup>20</sup> In the 1636-patient Ocular Hypertension Treatment Study (OHTS), topical ocular hypotensive medication was effective in delaying or preventing onset of POAG over 60 months of follow-up (POAG incidence was 4.4% in the treatment group vs 9.5% in the observation group; HR 0.40; 95% CI, 0.27-0.59;  $P < .001$ ).<sup>26</sup> Similarly, 48-month results of the Early Manifest Glaucoma Treatment study demonstrated a 49% risk of visual field progression in the control group versus a 30% risk of progression in the treatment group, corresponding with a treatment difference of 19% (95% CI, 7%-23%;  $P = .004$ ).<sup>27</sup> Results of the Ocular Hypertension Treatment Study and the Early Manifest Glaucoma Treatment study suggested a 10% risk reduction for every 1 mm Hg reduction in IOP.<sup>28,29</sup> More recently, in a follow-up analysis of data reported by Garway-Heath et al, it was estimated that each 1 mm Hg reduction in IOP reduced the risk of visual field deterioration by approximately 19%.<sup>30,27</sup> Results of several landmark randomized multicenter clinical trials demonstrating effects of IOP lowering in patients with POAG are summarized in [Table 1](#).<sup>20,23,26,27,30-33</sup>

IOP-lowering therapy is also effective at delaying progression of disease in patients without elevated IOP (NTG). NTG is characterized by ocular damage and vision loss at statistically normal IOP levels.<sup>23,24</sup> In the Collaborative Normal Tension Glaucoma Study, 140 patients with NTG received IOP-lowering medical or surgical treatment in 1 eye. When IOP was lowered by 30% (the treatment target in this study), the treated eyes had a slower rate of visual field progression than untreated eyes.<sup>23</sup>

### Unmet Needs in Glaucoma Therapy

As indicated above, most pharmacologic agents that lower IOP act by either reducing aqueous humor production or by increasing outflow/drainage of aqueous humor from the eye primarily through the uveoscleral pathway.<sup>2,14</sup> There is an unmet need for tolerable treatments that target the conventional (trabecular meshwork/Schlemm's canal) outflow pathway, and for therapies that target both conventional and unconventional outflow pathways. The

**FIGURE 1.** Aqueous Humor Outflow Pathways With Existing Agents<sup>19</sup>



Aqueous humor is produced by the ciliary body and secreted into the posterior chamber (yellow arrow). After bathing the lens, the aqueous humor circulates into the anterior chamber via the pupil (red arrow across iris), leaving the eye via the trabecular meshwork into Schlemm's canal (trabecular outflow), through the peripheral base of the iris into the ciliary body, and through the sclera (uveoscleral flow). Glaucoma therapies include agents that decrease aqueous humor inflow [eg, beta-blockers,  $\alpha_2$ -adrenergic receptor [AR] agonists, carbonic anhydrase inhibitors [CAIs]], enhance trabecular outflow, [eg, muscarinic agonists], or enhance uveoscleral outflow [eg, prostaglandin analogs].<sup>19</sup> Latanoprostene bunod reduces intraocular pressure by increasing the outflow of aqueous humor via both the trabecular meshwork and uveoscleral routes.<sup>50</sup> Reprinted by permission from Macmillan Publishers Ltd: *Pharmacogenomics J*, Copyright (2003).

trabecular meshwork tissue is diseased in glaucoma presenting increased resistance to aqueous outflow, and is therefore responsible for elevated IOP in POAG.<sup>17,34</sup> Current therapies do not target the conventional outflow pathway, leaving a potentially important modality for IOP reduction largely unused.<sup>34</sup>

Evaluation and treatment of IOP can be complicated by variability of IOP between eyes as well as diurnal and nocturnal variations. IOP tends to rise at night when individuals are supine, and peaks around 5:30 AM. Therefore, daytime office measurements may underestimate IOP levels, and may miss spikes in IOP.<sup>24</sup> With treatments administered during the morning hours, nocturnal IOP elevations may be uncontrolled, which may result in overestimation of treatment efficacy, uncontrolled IOP elevation, and an increased risk of glaucomatous damage.

**TABLE 1:** Studies Evaluating Effect of Lowering IOP on Glaucoma Onset or Progression<sup>20,23,26,27,30-33</sup>

Clinical Trial	Purpose	Patients	Design	Primary Significant Outcomes
Ocular Hypertension Treatment Study	Evaluate the safety and efficacy of ocular hypotensive treatment in preventing or delaying the onset of visual field or optic nerve damage	1636 patients with ocular hypertension	Multicenter RCT comparing observation with medical therapy	Topical ocular hypotensive medication effective in delaying or preventing onset of POAG; incidence of OAG after 60 months of follow-up was 9.5% in the observation group vs 4.4% in treatment group (HR 0.40; 95% CI, 0.27-0.59; $P < .001$ )
Early Manifest Glaucoma Trial	Evaluate efficacy of IOP reduction in preventing progression of glaucoma	255 patients with newly diagnosed OAG	Multicenter RCT comparing observation with betaxolol and argon laser trabeculoplasty	At a median 6 years follow-up, 62% of untreated eyes vs 45% of treated eyes showed progression ( $P = .007$ )
Advanced Glaucoma Intervention Study	Compare clinical outcomes of 2 treatment sequences in glaucoma; trabeculoplasty-trabeculectomy vs trabeculectomy-trabeculoplasty-trabeculectomy	789 eyes of 591 patients with medically uncontrolled OAG	Multicenter RCT comparing procedure sequences	Lower IOP was associated with less visual field loss during follow-up; eyes that had 100% of visits with IOP $< 18$ mm Hg (average IOP during follow-up of 12.3 mm Hg) had significantly ( $P = .016$ ) less visual field progression during follow-up than eyes with 50% to $< 75\%$ of visits with IOP $< 18$ mm Hg
Collaborative Initial Glaucoma Treatment Study	Compare medical vs surgical therapy as initial treatment	607 patients with newly diagnosed OAG	Multicenter RCT	IOP was lower in the surgical group; initial medical therapy resulted in similar visual field outcomes as surgery for up to 5 years of follow-up; minimal vision loss was observed in both groups over the study period
Collaborative Normal-Tension Glaucoma Study	Determine whether IOP is involved with optic nerve damage in NTG	140 patients with NTG	Multicenter randomized study comparing active treatment of lowering IOP by 30% and no treatment	Active treatment was associated with a longer time to disease progression ( $2688 \pm 123$ days) compared with no treatment ( $1695 \pm 143$ days)
United Kingdom Glaucoma Treatment Study	Efficacy of IOP lowering with latanoprost vs placebo for vision preservation	516 patients with newly diagnosed OAG	Multicenter RCT comparing active treatment with placebo	Visual field preservation was significantly longer in patients treated with IOP-lowering therapy compared with placebo at 24 months (HR 0.44; 95% CI, 0.28-0.69; $P = .0003$ ). This corresponds with a 19% reduction in visual field loss for every 1 mm Hg of IOP lowering

IOP indicates intraocular pressure; OAG, open-angle glaucoma; POAG, primary open-angle glaucoma; RCT, randomized controlled trial.

Another unmet need is the challenge of adherence in patients receiving complex glaucoma treatment regimens.<sup>35</sup> When a second prescription was added to an IOP-lowering regimen, prescription refills were delayed or decreased.<sup>36,37</sup> Adherence is expected to be better for simple regimens.<sup>36</sup> In one study of patients newly initiating prostaglandin therapy for glaucoma, 25% of patients received 1 or 2 prescription fills of adjunctive therapy added on to prostaglandin therapy. Of these patients, slightly more than one-fourth (26%) continued therapy with a different agent, and the remaining 74% discontinued therapy entirely.<sup>38</sup> In order to improve adherence to IOP-lowering therapy, there is a need for novel effective agents with simple treatment regimens (ie, once-daily dosing and single agent) for the management of glaucoma, especially in the population ineffectively

managed with combination therapies.<sup>36</sup> Patients may potentially achieve more consistent effects of treatment, and overall greater effectiveness in glaucoma management with convenient regimens.<sup>35</sup>

### Pharmacologic Options for Glaucoma Management

A reasonable objective for initial treatment of patients with POAG is to reduce IOP by 20% to 30% below baseline. This target IOP is an estimate of treatment needed to lower the risk of disease progression and protect vision. An IOP may be adjusted up or down, as indicated by risk factors present, stage of glaucomatous damage or disease severity, and progression or aggressiveness during long-term monitoring. Therefore, management in IOP reduction should be individualized to patient needs over the course of disease and is subject to change.<sup>2</sup>

Prostaglandin analogs are considered first-line therapy for POAG. They increase uveoscleral outflow, effectively lower IOP, are usually well-tolerated, can be dosed once a day, and also act during the night when IOP levels may be more elevated.<sup>39</sup> These agents bind to prostaglandin receptors; they alter the expression of matrix metalloproteinases (MMPs) and increase uveoscleral outflow, lowering IOP.<sup>14</sup>

Currently, latanoprost is the most prescribed prostaglandin analog in the United States.<sup>40</sup> In pivotal phase 3 trials of latanoprost conducted in the United States, the United Kingdom, and Scandinavia, latanoprost reduced baseline diurnal IOP over 6 months of treatment by a mean of 6.7 mm Hg, 8.5 mm Hg, and 8.0 mm Hg, respectively.<sup>41</sup> In a later trial evaluating the efficacy of latanoprost compared with placebo in lowering IOP and preserving vision, the treatment was evaluated in 516 patients with newly diagnosed open-angle glaucoma (OAG). At baseline, 44% of the treatment group and 49% of the control group had IOP levels  $\geq 20$  mm Hg. At 24 months, the mean reduction in IOP was 3.8 mm Hg in the latanoprost-treated group and 0.9 mm Hg in the placebo group. At 24 months, visual field preservation was significantly better in patients treated with IOP-lowering therapy compared with placebo (HR 0.44; 95% CI, 0.28-0.69;  $P = .0003$ ). None of the 18 serious adverse events observed in the latanoprost-treated group were attributed to the drug.<sup>30</sup>

The IOP lowering activity of prostaglandin analogs and other important classes of therapies used as single agents in the treatment of glaucoma is summarized in **Table 2**.<sup>2,19</sup> These agents include the following:

- Prostaglandin analogs act by increasing outflow through the uveoscleral (unconventional) pathway. Adverse events may include conjunctival hyperemia, hyperpigmentation of the iris and eyelashes, increased eyelash growth, blepharopigmentation, and prostaglandin-associated periorbitopathy.<sup>14</sup>
- Beta-adrenergic receptor antagonists (beta blockers) reduce IOP by decreasing the production and secretion of aqueous humor.<sup>14</sup> Potential adverse effects associated with beta-blocker treatment may impair adherence to therapy including depression, exercise intolerance, and allergic conjunctivitis or contact dermatitis. Adverse effects, such as hypotension, bradycardia, and bronchospasm may limit beta-blocker use in patients with these pre-existing conditions, as well as use in patients with chronic obstructive pulmonary disease or asthma.<sup>2</sup>

**TABLE 2:** Single-Agent Efficacy in Reduction of IOP<sup>2,19</sup>

Class	IOP reduction	Primary target		
		Unconventional outflow pathway (uveoscleral outflow pathway):	Conventional outflow pathway (TM and SC):	Decreases production of aqueous humor
Prostaglandin analogs (prostanoid FP receptor agonists)	25%-33%	Yes	No	No
Beta-adrenergic antagonists (beta-blockers)	20%-25%	No	No	Yes
Alpha-adrenergic receptor agonists	20%-25%	Yes	No	Yes
Oral carbonic anhydrase inhibitors	20%-30%	No	No	Yes
Parasympathomimetic agents (muscarinic agonists)	20%-25%	No	Yes	No
Topical carbonic anhydrase inhibitors	15%-20%	No	No	Yes

IOP indicates intraocular pressure; SC, Schlemm's canal; TM, trabecular meshwork.

- Alpha-2 adrenergic receptor agonists act on alpha adrenergic receptors, reducing the production of aqueous humor by the ciliary body, and increasing uveoscleral outflow to decrease IOP.<sup>14</sup> Alpha-2 adrenergic agonists are associated with potential adverse effects including allergic conjunctivitis or contact dermatitis and follicular conjunctivitis. Additional potential adverse effects include dry mouth and nose, headache, fatigue, or drowsiness and hypotension.<sup>2</sup>
- Both topical and systemic carbonic anhydrase inhibitors reduce production of aqueous humor by the epithelial cells within the ciliary body, thereby reducing IOP.<sup>14,17</sup> Both topical and oral carbonic anhydrase inhibitors are potentially limited as treatment options for patients with kidney stones, blood disorders and sulfonamide allergies. Potential adverse events differ between the use of oral or topical treatments; topical carbonic anhydrase inhibitors are associated with allergic dermatitis or conjunctivitis like other agents, as well as corneal conditions. Potential systemic treatment-related effects of oral carbonic anhydrase inhibitors include depression, anorexia, blood disorders, gastrointestinal upset, and adverse events related to kidney function (eg, renal calculi, serum electrolyte imbalance).<sup>2</sup>
- Direct and indirect cholinergic agonists are direct agonists of parasympathetic receptors in the ciliary muscle where they induce contractions that expand the trabecular meshwork and dilate Schlemm's canal, acting on the conventional



pathway to decrease aqueous humor outflow resistance.<sup>14,17</sup> However, these agents are used less frequently due to adverse events including, pupil constriction, eye pain, brow ache, and reduced night vision.<sup>14</sup>

Although single agents have demonstrated relative IOP reductions near the target IOP (20%-30% reduction from baseline), individual agent IOP-lowering efficacy differs. In a meta-analysis comparing IOP-lowering agents, the degree of IOP lowering demonstrated by single agents varied with peak and trough drug levels. The most substantial IOP reductions were achieved with prostaglandin analogs where relative IOP lowering was demonstrated from 28% to 33%. Beta-blockers reduced IOP by 20% to 27%, alpha-adrenergic receptor agonists reduced IOP by 18% to 25%, and carbonic anhydrase inhibitors reduced IOP by 17% to 22%.<sup>42</sup> As available single agents may require additional IOP-lowering to achieve IOP targets, treatment regimens that include adjunctive therapy are designed with different classes of medications for optimal IOP reduction.<sup>43</sup>

Use of combination therapies in patients with glaucoma is often required to achieve adequate control of IOP. For instance, a retrospective analysis of 16,486 patients with glaucoma who were using a prostaglandin analog showed that within 24 months of starting this therapy, 36% required 1 or more adjunctive therapies and 82% of them had started adjunctive therapy with a beta-blocker within 12 months of initiating prostaglandin analog treatment. Initial adjunctive therapies included a fixed-dose combination product in 28% of patients. Overall, 42% of patients required adjunctive therapy within 30 days.<sup>38</sup>

Fixed combinations of IOP-lowering medications have been shown to be more effective than the individual components and offer the advantages of enhanced convenience, improved adherence, reduced exposure to preservatives, and a possible lower cost. Additionally, some combinations are better tolerated than monotherapy.<sup>36</sup> However, a disadvantage of fixed-combinations of IOP-lowering medications is that there is no option for adjusting the strength of individual medications within the combination.

## Therapeutic Pipeline for Lowering IOP

Several IOP-lowering agents are in development to address the unmet therapeutic needs of patients with glaucoma, including the need for agents with new mechanisms of action, with better efficacy and with acceptable tolerability, as well as patient convenience. Key information about these agents is summarized below.

### Trabodendoson Alone and in Combination With Latanoprost

Trabodendoson is a highly selective adenosine A<sub>1</sub>-receptor agonist with a novel mechanism of action. It enhances the outflow of aqueous humor by upregulating MMP-2 expression in the trabecular

meshwork, resulting in remodeling of the extracellular matrix in that tissue, lowering outflow resistance and IOP. Across 144 patients with OHT or POAG enrolled in the trial, trabodendoson was well-tolerated at 4 doses tested (ie, 50 mcg, 100 mcg, 200 mcg, and 500 mcg daily) and reduced IOP significantly at the 500 mcg dose compared with placebo at all time points (9 AM, 10 AM, 12 PM, 4 PM, and 8 PM) tested on day 28 (mean intra-day IOP reduction: 1.15 mm Hg with placebo vs 4.1 mm Hg with trabodendoson 500 mg,  $P < .05$ ).<sup>44</sup> However, the first pivotal phase 3 trial of trabodendoson for treatment of POAG or OHT failed to meet the primary endpoint of superiority in reduction of IOP compared with placebo. Also notable, in a phase 2 trial of trabodendoson in combination with latanoprost, the combination failed to outperform latanoprost alone in IOP reduction.<sup>45</sup>

### Netarsudil Alone and in Combination With Latanoprost

Netarsudil is a member of a new class of IOP-lowering agents that inhibits Rho-kinase and norepinephrine transport. Through these mechanisms, netarsudil increases aqueous humor outflow through relaxation of the trabecular meshwork, decreases the production of aqueous humor, and decreases episcleral venous pressure. Netarsudil statistically lowers IOP in patients and is dosed once daily. A 29-day study randomly assigned 298 patients with POAG or OHT to single-agent latanoprost 0.005%, single-agent netarsudil 0.02%, or 1 of 2 concentrations of combinations of the 2 agents (ie, netarsudil 0.01%/latanoprost 0.005% or netarsudil 0.02%/latanoprost 0.005%). At day 29, reductions in mean diurnal IOP were 1.9 mm Hg greater for netarsudil 0.02%/latanoprost 0.005% versus latanoprost and 2.6 mm Hg greater versus single-agent netarsudil 0.02% ( $P < .0001$ , both comparisons). Conjunctival hyperemia was observed in approximately 40% of patients receiving either strength of the combination treatment, 40% of patients receiving single-agent netarsudil, and 14% in the latanoprost-only group.<sup>46</sup>

The fixed-dose combination netarsudil 0.02%/latanoprost 0.005% has been further studied in a 90-day phase 3 trial and a 12-month phase 3 registration trial. In the 90-day trial, the primary efficacy endpoint, statistical superiority of the combination over each component as a single agent, was achieved. Combination netarsudil/latanoprost dosed once daily lowered IOP by 1 to 3 mm Hg more than monotherapy with either netarsudil or latanoprost throughout the study. About 10% of patients in each arm discontinued. In patients receiving netarsudil/latanoprost, more than half (55%) of patients experienced mild hyperemia, the most common adverse event. There were no serious adverse events.<sup>47,48</sup>

Interim 3-month findings of the 12-month phase 3 study also indicate significantly greater reductions in IOP with netarsudil/latanoprost than with either treatment used alone at 2 weeks, 6 weeks, and 3 months of follow-up ( $P < .0001$ ). Moreover, 44% of patients receiving netarsudil/latanoprost achieved IOP levels

15 mm Hg or lower, versus 23% of patients receiving netarsudil and 25% of patients receiving latanoprost ( $P < .0001$ ). Conjunctival hyperemia was observed in 53% of patients receiving the combination therapy versus 41% of patients receiving netarsudil alone and 14% of patients receiving latanoprost alone. No serious drug-related adverse events were observed.<sup>48</sup> Preliminary 1-year results of this trial were reported on July 19, 2017. Results of the 1-year efficacy endpoint were similar to results at the 90-day efficacy endpoint, with 60% of patients receiving netarsudil/latanoprost achieving a mean IOP of 16 mm Hg or lower. Secondary endpoints of IOP measurements at certain time intervals also exceeded reductions of IOP of both latanoprost 0.05% and netarsudil 0.02% by a range of 1 to 3 mm Hg.<sup>49</sup> In terms of safety, the most common side effect with netarsudil/latanoprost was conjunctival hyperemia, present in 60% of patients, 70% of which were mild. Other adverse events, such as conjunctival hemorrhages and cornea verticillata were also consistent with the 90-day safety findings.<sup>49</sup>

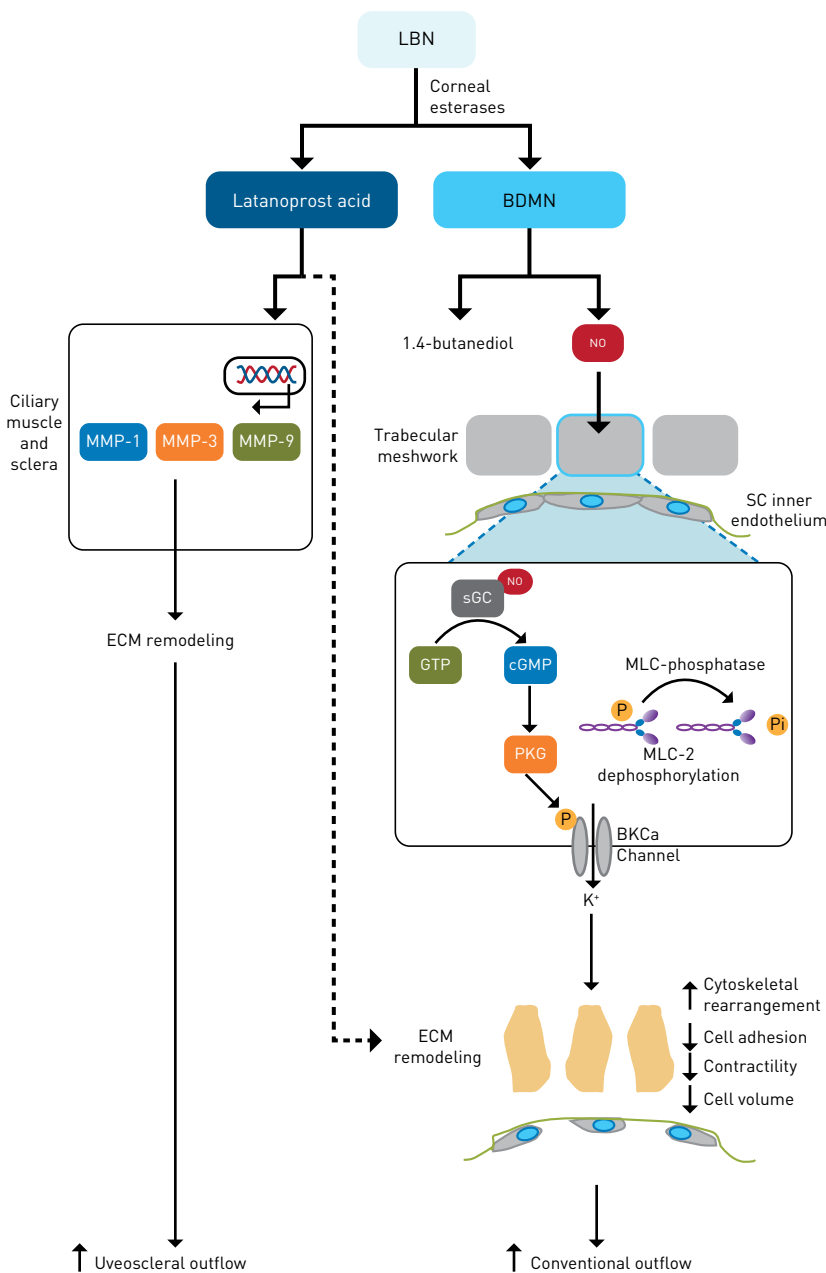
### Latanoprostene Bunod Mechanism of Action

Latanoprostene bunod (LBN) has a novel dual mechanism of action lowering IOP by acting on both of the major pathways for aqueous humor outflow, as shown in Figure 2.<sup>50</sup> When LBN is topically administered to the eye, it is hydrolyzed by endogenous esterases into latanoprost acid, the active component of latanoprost, and butanediol mononitrate, which breaks down into nitric oxide (NO) and inactive 1,4-butanediol.<sup>39,50-52</sup> This is illustrated in Figure 3.<sup>39,51,52</sup>

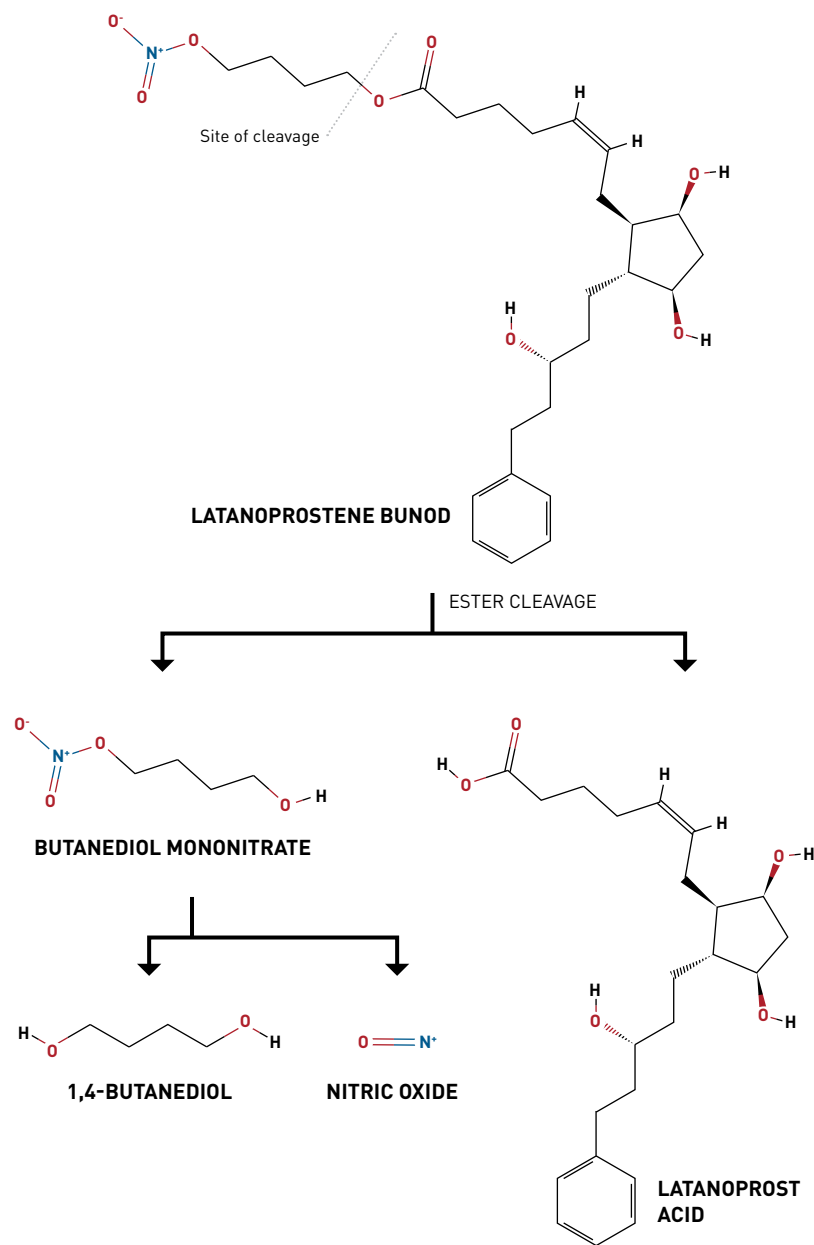
Latanoprost acid increases the outflow of aqueous humor by reducing resistance through the uveoscleral pathway, by enhancing MMP expression, and remodeling extracellular matrix in the ciliary muscle and sclera.<sup>50</sup> The unique NO component of LBN has an additional important effect on the conventional outflow pathway and adds a new mechanism of action to available treatment options unique from that of latanoprost and other prostaglandin analogs.<sup>50</sup>

Nitric oxide is an endogenous signaling molecule with a wide range of physiological

FIGURE 2. Novel Dual Mechanism of Action of Latanoprostene Bunod<sup>50</sup>



Putative mechanism of action of latanoprostene bunod (LBN). When LBN is applied to the surface of the eye, LBN is hydrolyzed by esterases into latanoprost acid and butanediol mononitrate (BDMN). Latanoprost acid increases expression of matrix metalloproteinases (MMPs) in the ciliary muscle, which promotes remodeling of the ciliary muscle extracellular matrix (ECM) and increased aqueous humor outflow through the uveoscleral route. MMPs may also increase conventional outflow through Schlemm's canal (SC) via remodeling of the trabecular meshwork (TM; minor pathway, dashed arrow) albeit to a much lesser degree. Nitric oxide (NO) released from BDMN enters TM cells and the inner SC wall, resulting in dephosphorylation of myosin light chain-2 (MLC-2) and efflux of potassium ions (K<sup>+</sup>) through large-conductance calcium-activated potassium (BKCa) channels. This, in turn, decreases cell contractility and volume, and promotes rearrangement of the actin cytoskeleton, altering the biomechanical properties of TM and SC cells and increasing conventional outflow.<sup>50</sup> cGMP indicates cyclic guanosine monophosphate; GTP, guanosine triphosphate; P, phosphate; Pi, inorganic phosphate; PKG, protein kinase G; sGC, soluble guanylate cyclase. Reprinted with permission from Society for Clinical Ophthalmology (Great Britain).<sup>50</sup>

**FIGURE 3.** Metabolic Activation of Latanoprostene Bunod<sup>39,51,52</sup>

Metabolism of latanoprostene bunod (LBN) to latanoprost acid (1) and nitric oxide (2). Following topical ocular administration, LBN undergoes carboxyl ester hydrolysis to latanoprost acid (1) and butanediol mononitrate, which is subsequently reduced to 1,4-butanediol and nitric oxide (2).<sup>39</sup>

functions including its well-known role as a mediator of smooth muscle relaxation and vasodilation. Generation of NO by nitric oxide synthases (NOS) leads to activation of soluble guanylate cyclase (sGC), resulting in increased levels of cyclic guanosine monophosphate (cGMP) and activation of protein kinase G. Resulting effects on cyclic nucleotide gated channels, protein kinases, and

other molecules lead to actin cytoskeletal rearrangement and thus cell relaxation culminating in physiological outcomes.<sup>53</sup>

The NO-sGC-cGMP signaling pathway appears to control physiological IOP via regulation of aqueous humor outflow. In the healthy human eye, NOS are present in the trabecular meshwork, Schlemm's canal, uveal vascular endothelium, the ciliary body, and nerve fibers in the limbus cornea and lens epithelium.<sup>53</sup> In patients with POAG, markers for NO are decreased in aqueous humor, suggesting lower NO levels may contribute to increased IOP.<sup>53</sup> There is some evidence that low-level NO signaling may have neuroprotective effects in glaucoma, and may also act by regulating episcleral blood flow.<sup>53</sup> The glaucoma medication nipradilol, which is not available in the United States, has an NO-donating effect in addition to its alpha and beta receptor blocking activity, and reduces retinal ganglion cell death compared with a control when administered to rats with experimentally damaged optic nerves.<sup>53,54</sup>

NO is thought to mediate its IOP-lowering effects by activation of the sGC/cGMP/protein kinase G pathway as described previously in other tissues. This, in turn, promotes rearrangement of the actin cytoskeleton resulting in decreased cell contractility and volume in the trabecular meshwork and Schlemm's canal. These changes alter the physical properties of the trabecular meshwork and Schlemm's canal cells, resulting in an increase in conventional outflow and lower IOP.<sup>50</sup>

### Preclinical Studies of LBN

LBN reduced IOP by 17% in wild-type mice and by 0.45 mm Hg to 1.23 mm Hg in an FP-receptor knockout mouse model insensitive to the action of prostaglandin analogs.<sup>55</sup> In a canine model of glaucoma, LBN decreased IOP by 44% from baseline versus latanoprost, which reduced IOP by 27%.<sup>56</sup> In nonhuman primates with elevated

IOP, reduction of IOP was greater with LBN (31%-35% depending on dose) than with latanoprost (25.8%).<sup>56</sup> Additionally, in a rabbit model, LBN reduced the hypertensive response induced by injecting hypertonic saline intravitreously, while the same dose of latanoprost was without effect.<sup>56</sup> These results, in part, formed the rationale for clinical trials of LBN, which are discussed in the next section.



**TABLE 3:** Key Studies of Efficacy Evaluations of Latanoprostene Bunod<sup>39,50,51,57-59</sup>

Trial	Patients	Design	Reduction of IOP	P value	Responders Target IOP	P value
VOYAGER	N = 413 with OHT or OAG (ITT)	Phase 2 RCT of LBN doses 0.006%, 0.012%, 0.024%, 0.040% and latanoprost 0.005%; for 28 days	LBN 0.024% (n = 83) change from baseline was -9 mm Hg with LBN (from baseline of 26.01 mm Hg) vs -7.77 mm Hg with latanoprost (from baseline of 26.15 mm Hg) at day 28	<i>P</i> = .009 from baseline for LBN 0.024% group; <i>P</i> = .005 for day 28 difference between LBN 0.024% and latanoprost	LBN 0.024% group had more subjects with mean diurnal IOP ≤18 mm Hg at day 28 vs latanoprost	<i>P</i> ≤ .046
APOLLO	N = 417 with OAG or OHT (ITT)	Phase 3 RCT; assigned 2:1 LBN 0.024% vs timolol 0.05% for 3 months, all patients received LBN for an additional 9 months	Mean range for change from baseline was -7.7 to -9.1 mm Hg with LBN 0.024% (from baseline of 26.7 mm Hg) vs -6.6 to -8.0 mm Hg with timolol (from baseline of 26.5 mm Hg). Mean IOP range of 17.8-18.7 mm Hg for LBN vs 19.1-19.8 mm Hg for timolol at 3 months. Diurnal IOP of 18.2 mm Hg for LBN vs 19.4 mm Hg for timolol at 3 months.	<i>P</i> ≤ .002 for both mean range for change from baseline and mean IOP <i>P</i> < .001 for mean diurnal IOP	IOP reduction ≥25%: 34.9% LBN vs 19.5% timolol	<i>P</i> = .001
LUNAR	N = 414 with OAG or OHT (ITT)	Phase 3 RCT: 2:1 LBN 0.024% vs timolol 0.5% for 3 months, all patients received LBN for an additional 3 months	Mean range for change from baseline was -7.5 to -8.8 mm Hg with LBN 0.024% (from baseline of 26.6 mm Hg) vs -6.6 to -7.9 mm Hg with timolol (from baseline of 26.4 mm Hg). Mean IOP range 17.7-18.7 mm Hg for LBN vs 18.8-19.6 mm Hg for timolol. Mean diurnal IOP of 18.1 mm Hg for LBN vs 19.3 mm Hg for timolol at 3 months	<i>P</i> ≤ .025 for both mean range for change from baseline and mean IOP <i>P</i> ≤ .034 for mean diurnal IOP	IOP reduction ≥25%: 31% LBN vs 18.5% timolol	<i>P</i> = .007
JUPITER	N = 130 with OAG or OHT (enrolled)	Phase 3 open-label; LBN 0.024% for 52 weeks	Mean IOP at week 52 was 14.4 mm Hg for both eyes from baseline of 19.6 mm Hg for study eyes and 18.7 mm Hg for fellow treated eyes	<i>P</i> < .001 vs baseline		

IOP indicates intraocular pressure; ITT, intent to treat; LBN, latanoprostene bunod; OAG, open-angle glaucoma; OHT, ocular hypertension; RCT, randomized, controlled trial.

### Latanoprostene Bunod Key Clinical Trials

The clinical development program for LBN is summarized below. Results of key efficacy evaluations of LBN are summarized in [Table 3](#).<sup>39,50,51,57-59</sup>

#### Phase 1 Trial of LBN

KRONUS was a phase 1, single-center, open-label clinical study in 24 healthy Japanese male volunteers treated for 14 days with LBN 0.024% administered once every evening. Subjects had their 24-hour IOP profiles assessed in a sleep lab at baseline and after 14 days of dosing. LBN significantly reduced IOP at all evaluated time points (*P* < .001), with a mean 24-hour reduction of 3.6 (standard deviation = 0.8) mm Hg (27%) from baseline. Common adverse events included mild punctate keratitis and ocular hyperemia.<sup>60</sup>

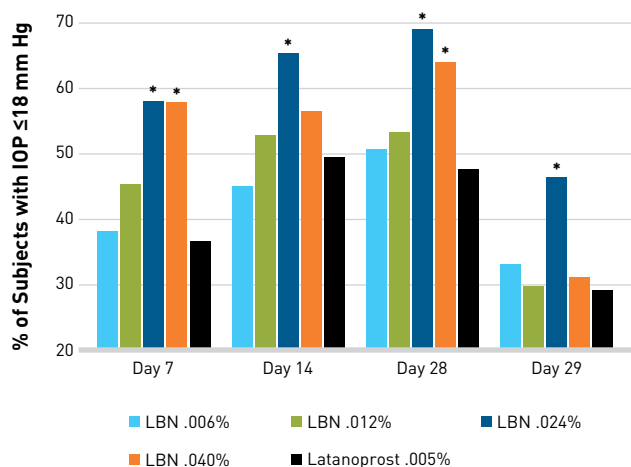
#### Phase 2 Trials of LBN

VOYAGER was a phase 2, multicenter, randomized, controlled, investigator-masked, dose-finding trial in 413 patients with OAG or OHT. Patients were randomly assigned to LBN 0.006% (n = 82),

LBN 0.012% (n = 85), LBN 0.024% (n = 83), LBN 0.040% (n = 81), or latanoprost 0.005% (n = 82). Each treatment was administered once daily in the evening for 28 days. Efficacy for LBN was dose-dependent, plateauing at the 0.024% and 0.040% doses.<sup>57</sup> At the primary efficacy endpoint of day 28, treatment with LBN 0.024% resulted in a mean IOP reduction of 9.00 mm Hg compared with a 7.77 mm Hg reduction with latanoprost treatment, for a statistically significant treatment difference of 1.23 mm Hg (*P* = .005).<sup>57</sup> LBN 0.024% was also associated with significantly greater reductions in diurnal IOP compared with latanoprost on days 7 (*P* = .033) and 14 (*P* = .015).<sup>57</sup>

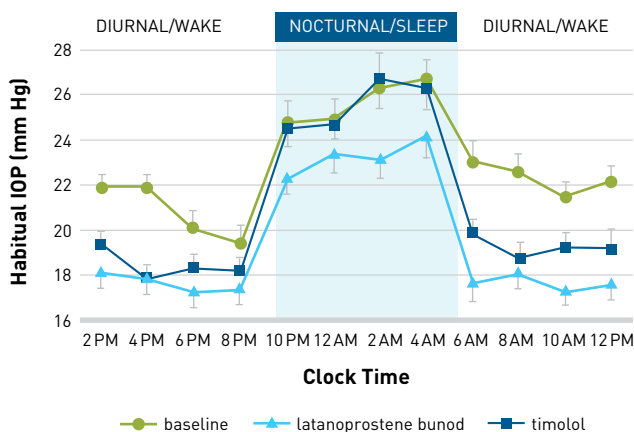
At all follow-up visits over the 29-day assessment period, a significantly greater proportion of patients treated with LBN 0.024% achieved a mean diurnal IOP of ≤18 mm Hg compared with patients receiving latanoprost (*P* ≤ .046). A significantly greater proportion of patients within the LBN 0.040% treatment group achieved a mean IOP of ≤18 mm Hg measured during visits on day 7 and day 28 compared with patients in the latanoprost group (*P* = .007 and *P* = .039, respectively), as shown in [Figure 4](#).<sup>57</sup>

**FIGURE 4.** Percentage of Patients Achieving Target IOP Levels<sup>57</sup>



\*P < .05 versus latanoprost.  
LBN, latanoprostene bunod.  
Reprinted with permission from *British Journal of Ophthalmology*.<sup>57</sup>

**FIGURE 5.** Reductions in Habitual IOP Over 24 Hours<sup>61</sup>



Profile of 24-hour habitual intraocular pressure (IOP). Measurements from 21 subjects sitting during the diurnal/wake period and supine during the nocturnal/sleep period (ie, habitual IOP). Open circles: baseline; solid triangles: after 4-week treatment with latanoprostene bunod 0.024% once daily; solid squares: after 4-week treatment with timolol 0.5% solution twice daily. Error bars represent standard error of the mean.<sup>61</sup>  
Reprinted from *American Journal of Ophthalmology*. 169. Liu et al. Efficacy of Latanoprostene Bunod 0.024% Compared With Timolol 0.5% in Lowering Intraocular Pressure Over 24 Hours. 249-257. Copyright (2016), with permission from Elsevier.

In the VOYAGER trial, of the patients treated with 0.024% LBN, 19.3% experienced at least 1 ocular treatment-related adverse event compared with 12.2% of patients treated with latanoprost 0.005%. The most frequent adverse events with LBN 0.024% were conjunctival hyperemia (4.8%), eye irritation (3.6%), and ocular hyperemia (2.4%). These adverse events were observed at a rate of 0%, 0%, and 8.5%, respectively, in patients receiving latanoprost.<sup>57</sup>

CONSTELLATION was a phase 2, single-center, randomized, controlled, open-label, 2-period crossover study in 25 patients (21 of whom completed the study) with OHT or early POAG. Patients were randomly assigned to bilateral treatment with LBN once in the evening or to timolol every 12 hours in the morning and evening. Patients crossed over to the comparator arm after 4 weeks for an additional 4 weeks of treatment. Similar to KRONUS, subjects had their 24-hour IOP profiles assessed in a sleep lab at baseline and at the conclusion of each 4-week treatment period.<sup>61</sup>

Although both LBN and timolol reduced diurnal IOP (measured in both the sitting and supine positions) by 2.3 to 3.9 mm Hg versus baseline ( $P < .001$ ), nocturnal IOP levels in patients receiving timolol were unchanged from baseline.<sup>61</sup> In contrast, patients treated with LBN achieved significant reductions in IOP over the entire 24-hour assessment period, as shown in Figure 5.<sup>61</sup> Nocturnal IOP with LBN was  $2.5 \pm 3.1$  mm Hg (mean  $\pm$  SD) less than baseline ( $P = .002$ ) and  $2.3 \pm 3.0$  mm Hg (mean  $\pm$  SD) less than timolol ( $P = .004$ ).<sup>61</sup> LBN treatment was also associated with greater diurnal sitting and supine OPP relative to baseline ( $P \leq .006$ ) and greater nocturnal OPP relative to timolol ( $P = .010$ ).<sup>61</sup>

### Phase 3 Trials of LBN

APOLLO was a phase 3 multicenter, randomized, double-masked, parallel-group study in 420 patients with OAG or OHT (387 patients completed the study).<sup>58</sup> The trial consisted of an initial 3-month active-controlled efficacy phase, followed by a 9-month open-label safety extension phase. The primary objective of the efficacy phase was to evaluate the non-inferiority of LBN 0.024% instilled once every evening compared with timolol 0.5% instilled twice daily for mean IOP reductions measured at 9 assessments performed at 8 AM, 12 PM, and 4 PM at each of 3 study visits: week 2, week 6, and month 3. The secondary objective was to assess the superiority of LBN versus timolol.<sup>58</sup>

The APOLLO trial results demonstrated not only the noninferiority of LBN 0.024% compared with timolol 0.5% for the primary outcome, but significantly greater mean IOP reductions to timolol at each time point throughout the 3-month double-masked treatment period.<sup>58</sup> At all 9 assessment time points, mean IOP was significantly lower in the LBN 0.024% group (17.8 to 18.7 mm Hg) than in the timolol 0.5% group (19.1 to 19.8 mm Hg;  $P \leq .002$ ). At all 9 time points, the percentage of patients with a mean IOP  $\leq 18$  mm Hg was significantly higher in the LBN group than in the timolol group (22.9% vs 11.3%;  $P = .005$ ), as was the percentage with IOP reduction of  $\geq 25\%$  (34.9% vs 19.5%;  $P = .001$ ).<sup>58</sup> IOP levels at all assessment points are presented in Figure 6.<sup>58</sup>

Notably, in APOLLO, the patient group receiving LBN 0.024% treatment had significantly lower mean diurnal IOP (average of IOP measured at 8 AM, 12 PM, and 4 PM) compared with timolol 0.5% treatment group at each study visit ( $P < .001$ , for all visits); LBN 0.024% demonstrated significantly greater reductions in mean diurnal

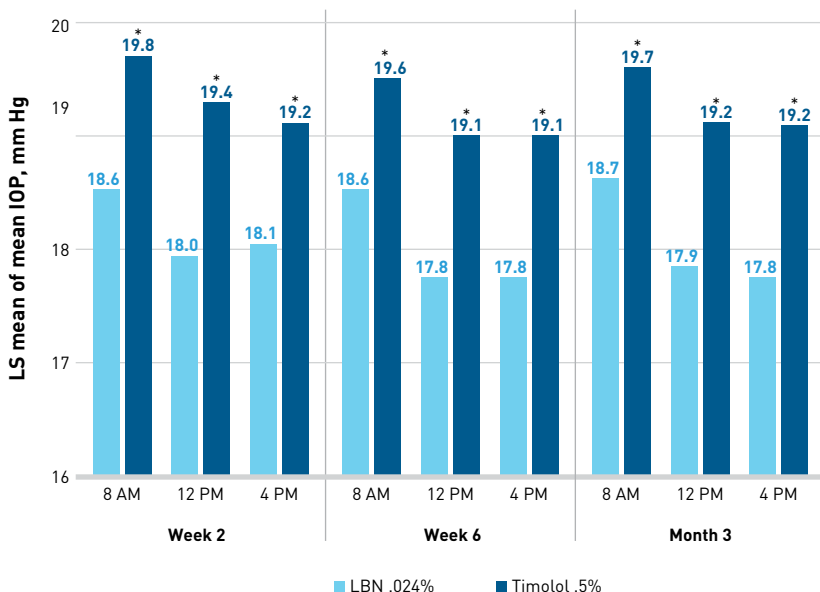
IOP compared with 0.5% timolol treatment at follow-up visits at week 2 (18.2 vs 19.5 mm Hg,  $P < .001$ ), week 6 (18.1 vs 19.3 mm Hg,  $P < .001$ ) and month 3 (18.2 vs 19.4 mm Hg,  $P < .001$ ).<sup>58</sup>

LUNAR was a phase 3, multicenter, randomized, controlled, double-masked study in 420 patients (of whom 387 completed the study) with OAG or OHT. The study design was identical to that of the APOLLO except that the open-label extension phase was 3 months in duration. Patients were randomly assigned 2:1 to LBN 0.024% once every evening or to timolol 0.5% twice daily for 3 months.<sup>59</sup> The primary objective of this study was to evaluate the noninferiority of the IOP lowering effect of LBN 0.024% over 3 months of treatment to that of timolol 0.5%. If noninferiority of LBN was achieved, the secondary objective was to evaluate the statistical superiority of LBN to timolol.<sup>59</sup>

Analysis of covariance showed that the mean IOP reduction with LBN was noninferior to timolol and was significantly greater than that with timolol ( $P \leq .025$ ) at all but the first time point in the study (week 2, 8 AM).<sup>59</sup> IOP was reduced  $\geq 25\%$  from baseline in 31.0% of patients treated with LBN and in 18.5% of patients treated with timolol ( $P = .007$ ). Reduction of IOP to  $\leq 18$  mm Hg over all timepoints/visits in the study did not differ significantly between treatment arms, occurring in 17.7% of the LBN-treated patients versus 11.1% of timolol-treated patients ( $P = .084$ ).<sup>59</sup> Mean diurnal IOP was significantly lower ( $P \leq .034$  at all timepoints) in the LBN group than in the timolol group (18.6 mm Hg vs 19.2 mm Hg [week 2], 18.2 mm Hg vs 19.1 mm Hg [week 6], 18.1 mm Hg vs 19.3 mm Hg [month 3]).<sup>59</sup> Mean changes in mean IOP are presented by treatment and study visit in **Figure 7**.<sup>59</sup>

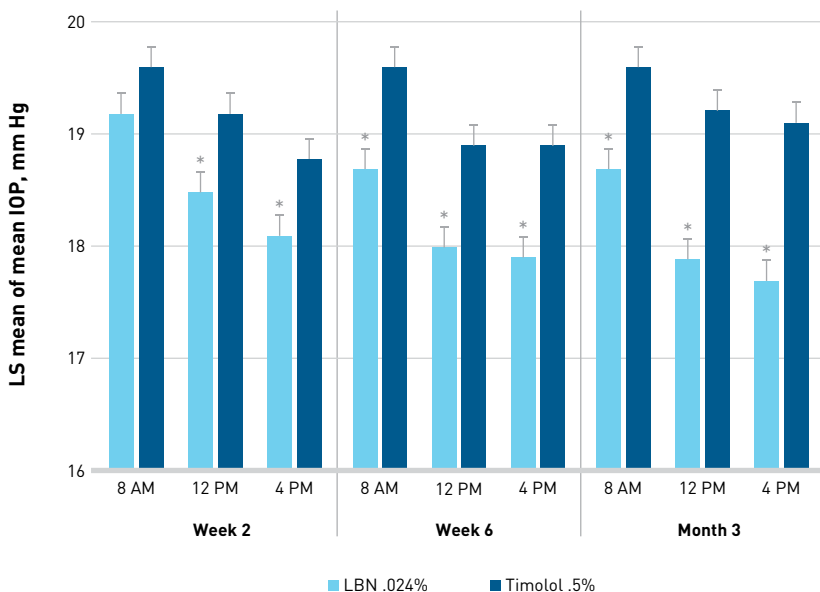
The American Academy of Ophthalmology Practice guidelines recommend an initial IOP target of at least a 25% reduction in patients with POAG.<sup>2</sup> In a post hoc pooled analysis of data from the combined APOLLO and LUNAR studies, a significantly greater proportion of patients treated with LBN achieved target IOP reductions of at least 25% from baseline at the 3 month evaluation time point than did patients treated with timolol (90% vs 79.6%;  $P < .0001$ ). A total of 60.5% of patients treated

**FIGURE 6.** Mean IOP in the APOLLO Study by Treatment Group, Visit, and Timepoint<sup>58</sup>



\* $P \leq .002$  versus timolol at the same assessment point. Bar chart indicates least squares mean IOP levels in study eye by visit, time point, and treatment group defined as the ITT population with LOCF.<sup>58</sup> IOP indicates intraocular pressure; ITT, intent to treat; LBN, latanoprostene bunod; LOCF, last observation carried forward. Reprinted from *Ophthalmology*.<sup>58</sup>

**FIGURE 7.** Mean IOP in the LUNAR Study by Treatment Group, Visit, and Timepoint<sup>59</sup>



\* $P \leq .025$  versus timolol at the same assessment point. Bar chart indicates least squares mean IOP levels in study eye by visit, time point, and treatment group defined as the ITT population with LOCF.<sup>59</sup> IOP indicates intraocular pressure; ITT, intent to treat; LBN, latanoprostene bunod; LOCF, last observation carried forward. Reprinted from *American Journal of Ophthalmology*, 168. Medeiros, et al. Comparison of Latanoprostene Bunod 0.024% and Timolol Maleate 0.5% in Open-Angle Glaucoma or Ocular Hypertension: The LUNAR Study. 250-259. Copyright (2016), with permission from Elsevier.

with LBN experienced reductions of IOP of at least 35% compared with 44.2% of timolol-treated patients ( $P < .0001$ ).<sup>62</sup>

Long-term efficacy and safety were assessed in patients in the open-label extension phases of the APOLLO and LUNAR studies. In the extension phase of both studies, patients treated with LBN during the efficacy phase maintained consistently lowered IOP. Patients randomly assigned to timolol during the efficacy phase had additional 6.3% to 8.3% decreases in mean diurnal IOP when crossed over to LBN treatment which were statistically significant ( $P \leq .001$  vs month 3 for APOLLO;  $P < .001$  vs month 3 for LUNAR).<sup>63,64</sup> Mean percent reduction in diurnal IOP during the extension phase when all patients were treated with LBN ranged from 32% to 34% from baseline ( $P < .001$  vs baseline).<sup>63,64</sup>

A pooled analysis of safety data from the APOLLO and LUNAR studies encompassed safety assessments throughout the 3-month efficacy phases of LBN 0.024% compared with timolol 0.5%, as well as the safety extension phases where patients enrolled in the continued treatment with LBN 0.024% for an additional 3 months in the LUNAR trial and 9 months in the APOLLO trial.<sup>65</sup> Overall, no safety concerns related to visual acuity or ocular signs were found. Of the safety population, 17.8% of patients treated with LBN throughout the study experienced treatment-related ocular adverse events compared with 11.1% of patients treated with timolol 0.5%. Treatment-emergent ocular adverse events were more common in the LBN treatment group than in the timolol group including conjunctival hyperemia (5.9% vs 1.1%), eye irritation (4.6% vs 2.6%), eye pain (3.6% vs 2.2%), and ocular hyperemia (2.0% vs 0.7%), respectively.<sup>65</sup>

JUPITER was a phase 3, multicenter, single-arm, open-label, 1-year study of LBN 0.024% instilled once daily in the evening in 130 Japanese patients. All patients participating in the study had OAG or OHT and the mean baseline IOP was 19.6 mm Hg. A total of 121 patients completed the study.<sup>51</sup> The 22.0% reduction in IOP from baseline observed by week 4 of the study was sustained through 1 year, at which point the average reduction in IOP from baseline was 26.3%.<sup>51</sup> At all 13 time points evaluated, average IOP was significantly ( $P < .001$ ) lower than at baseline by average margins ranging from 4.3 to 5.3 mm Hg.<sup>51</sup> In the JUPITER study, 47.7% of patients experienced 1 or more treatment-related ocular adverse event. The most common treatment-emergent ocular adverse events observed in this study included conjunctival hyperemia (17.7%), eyelash growth (16.2%), eye irritation (11.5%), eye pain (10.0%), iris hyperpigmentation (3.8%), and blepharal pigmentation (3.1%).<sup>51</sup> Overall, the safety profile of LBN was consistent across the phase 3 trials, with an AE profile similar to that of prostaglandin analogs.<sup>39,14</sup>

## Conclusions and Relevance

As of this writing, current agents used to reduce IOP by increasing aqueous humor outflow primarily target the uveoscleral pathway, rather than the conventional outflow pathway, the trabecular meshwork/Schlemm's canal. In terms of adherence, a major unmet

need remains for a single agent that is safe with robust and sustained efficacy that can be used once daily to improve the consistency of treatment adherence in patients with glaucoma. Treatments in development for management of POAG include trabodensin and netarsudil, both of which were also tested in combination with latanoprost, as well as LBN. The latter is expected to receive FDA marketing authorization in 2017 under the trade name of Vyzulta<sup>TM</sup> (latanoprostene bunod ophthalmic solution 0.024%) for reduction of IOP in patients with OAG or ocular hypertension.

LBN is the first and only NO-donating prostaglandin monotherapy that acts through 2 distinct mechanisms of action to reduce IOP. It directly targets both aqueous humor outflow pathways, facilitating outflow through the trabecular meshwork/Schlemm's canal (via NO) and through the uveoscleral pathway (via latanoprost acid).

Clinical study results demonstrated that LBN 0.024% provided superior IOP lowering to latanoprost, the current standard of care, in a phase 2 study, and consistent IOP lowering ranging from 7.5 to 9.1 mm Hg from baseline in the phase 3 APOLLO and LUNAR studies. Moreover, a single daily dose of LBN 0.024% not only provided 24-hour IOP control, but maintained lowered IOP when dosed for 1 year, both in patients with elevated IOP at baseline and in patients with low IOP at baseline. Together with its safety profile similar to that of other prostaglandin analogs, LBN 0.024% may therefore address the need for a single IOP-lowering agent that is safe, with efficacy that impacts the conventional outflow pathway and uveoscleral outflow. With its dual mechanism of action delivered through once-daily administration in the evening, LBN 0.024% may offer patients a better chance of treatment adherence, long-term treatment continuation, and, ultimately, therapeutic success. ■

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**Author affiliations:** Columbia University, New York, NY; University of Arizona College of Pharmacy, Tucson, AZ.

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